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<b>(21) International Application Number:</b> PCT/FI98/00284 <b>(22) International Filing Date:</b> 30 March 1998 (30.03.98)  <b>(30) Priority Data:</b> PO 8210 25 July 1997 (25.07.97) AU  <b>(71) Applicant (for all designated States except US):</b> CULTOR CORPORATION [FI/FI]; Kyllikimportti 2, FIN-00240 Helsinki (FI).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> CHAMPBELL, Roger [AU/AU]; 174 Hume Street, Corowa, NSW 2646 (AU).  <b>(74) Agent:</b> KOLSTER OY AB; Iso Roobertinkatu 23, P.O. Box 148, FIN-00121 Helsinki (FI).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> With international search report.
<b>(54) Title:</b> A PROPHYLACTIC  <b>(57) Abstract</b>  The invention relates to the use of prophylactics, especially betaines or related compounds, to enhance the resistance of animals to infection by mycoplasma or other organisms causing similar damage and/or reduce the amount of damage done to the animal by the infection. Also disclosed are animal feed compositions comprising said prophylactic agents for the use mentioned.		

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## A Prophylactic

The present invention relates generally to prophylactics, which are defined as substances useful for defending or protecting living things from being infected by and/or damage from disease, and include substances such as chemical compounds, compositions, materials and the like, and particularly to prophylactics useful in animal husbandry and in particular to methods and treatments for improving or enhancing the health and/or growth of animals. More particularly, the present invention relates to methods of and treatments for reducing the adverse effects of illness in animals, particularly the deleterious effects of mycoplasma-induced diseases and related conditions in pigs by administering the prophylactic. In particular, the present invention relates to methods and treatments for improving or enhancing the animals' resistance against diseases induced by mycoplasma and related organisms by administering betaine to the animals, particularly as part of a feed supplement, so that the treated animals are less prone to being infected by mycoplasma and there is significant improvement in the growth of the pigs. The present invention finds particular application in administering glycine betaine or equivalent chemical compounds either alone or in combination with other additives to pigs in predetermined dosages or amounts over or for a predetermined time interval by including the betaine in the feed of the pigs during growth to eliminate or reduce the damage caused by mycoplasmal infection.

Although the present invention will be described with particular reference to the use of glycine betaine, hereinafter referred to as betaine for ease of description, as one example of the prophylactic administered to pigs during their growth phase to significantly increase the health of the pigs by increasing their resistance to the effects of mycoplasma-induced diseases, it is to be noted that the scope of the present invention is not restricted to the described embodiments, but rather the present invention is more extensive in scope so as to include the use of other chemical materials, to other ways of administering the chemicals, and to other uses of the prophylactics than as described.

The cost of growing pigs to maturity ready for market is considerable and for economic pig production it is essential that each animal matures quickly in as healthy a condition as possible, which includes the pig

being as disease free as possible. One disease or condition suffered by pigs relates to infection by mycoplasma or related organisms, such as for example one or more of the other mycoplasmal infections. Infection by one or more of the mycoplasma-induced diseases causes great economic hardship to farmers and the profit-robbing capabilities of these insidious diseases have been known for years. Although vaccinations against these diseases have been developed over the last five years, treatments based on the vaccinations have not been successful for a variety of reasons and these diseases are still prevalent due in part to the complexity of the mycoplasmal infections since there are at least three different recognised mycoplasma species of bacteria that cause disease in pigs - Mycoplasma hyopneumoniae, Mycoplasma hyorhinis and Mycoplasma hyosynoviae.

Mycoplasmal pneumonia or porcine enzootic pneumonia, one of the more prevalent and insidious mycoplasmal diseases suffered by pigs, is caused by Mycoplasma hyopneumoniae, a mycoplasma which colonises in hair-like projections called cilia which line the pig's respiratory tract. The disease becomes doubly potent when the cilia are destroyed, as this opens the way for more-deadly secondary invaders to attack the pig, such as Pasteurella multocida and Actinobacillus pleuropneumonia, Haemophilus suis, Bordetella bronchiseptica, Actinomyces pyogenes, Streptococci, Staphylococci and viruses which often exacerbate the situation into a severe pneumonia attack.

Infection with mycoplasmal pneumonia is widespread, with some researchers calculating its prevalence at about 70% or even higher in swine herds, particularly in the United States. It is spread by direct contact between the animals as well as through the air. Pigs of any age are susceptible to the infection starting with those as young as 7-10 days of age, but symptoms of the disease are not normally exhibited until after 3 to 10 weeks of age. Mycoplasmal pneumonia is a chronic disease and even though a high percentage of pigs are affected by this disease, loss of pigs through death due to the disease is very low. In general, pigs with mycoplasmal pneumonia continue to eat reasonably well, but do not grow at a normal rate if lesions are extensive or secondary bacterial pneumonias occur. The more severe the lesions, the greater the effect of growth retardation or the like. Costs to the farmers associated with infection by mycoplasmal pneumonia vary as widely as the disease and animals infected with this disease exhibit slowed and

uneven growth, decline in feed efficiency and the like. Additionally, the infection lowers the pig's resistance to other diseases so that the animal becomes more susceptible to infection from other organisms, often with disastrous results. Measuring the weight of an individual pig at regular  
5 intervals is one way of monitoring the growth of the pig and can be used to record the effects of mycoplasmal infection.

In the past there have been many attempts to treat or cure this disease but unfortunately at present adequate treatment of established mycoplasmal pneumonia is not available. Therefore, there is a need to reduce  
10 the chances of animals in general and pigs in particular contracting mycoplasmal infection or to lessen the effect of this disease, particularly the damage to the lungs of the animal, in the event that it is infected.

A second mycoplasma affecting pigs, typically pigs weighing in the range from 7 to 30 kg, is Mycoplasma hyorhinis which causes arthritis and  
15 inflammation of the lining of the chest and abdominal cavity and membrane which covers the heart, as well as the membranes around the testicles of male pigs being affected. Typically, the animal infected by this disease has lesions around the lungs, heart or in the abdominal cavity. Again, there is no satisfactory treatment of this disease on an individual basis. The effect of this  
20 disease can be monitored by measuring the weight of the animal as well as inspecting the condition of the lungs when the animal is slaughtered. If an individual pig fails to gain weight or has only a small increase in weight over the period it is being monitored, this is an indication that the pig is suffering from some disease or other.

25 The third mycoplasma, Mycoplasma hyosynoviae, causes arthritis in larger pigs weighing 40 to 100 kg, which results in the pigs becoming very lame with swollen hock, elbow, shoulder or stifle joints. Although some treatments for this disease are known, the efficacy of such treatments is poor and about the only real method of eliminating mycoplasmal infections of this  
30 type from a swine herd is through depopulation and restocking with animals known to be free of these diseases. This is an extremely costly and time consuming exercise.

Thus, there is a great need to prevent animals, especially pigs, from being infected by one or more of the mycoplasma strains or related organisms  
35 which are responsible for the debilitating diseases discussed above and to

reduce the effects of any damage caused to animals by the mycoplasmal infection suffered by the animals.

Betaine has been used in the past as a feed supplement for piglets and growing pigs to improve the growth and carcass quality of the pigs.  
5 However, no investigations have been conducted to determine the effect of betaine in combating mycoplasmal infections in pigs, particularly in growing pigs. Surprisingly, it has been discovered that the use of betaine, particularly in predetermined amounts in feed stock, has resulted in significant improvement in the growth of pigs when exposed to infection by mycoplasma  
10 and/or when actually infected by these organisms. Even though betaine may have been used in the past in connection with pigs, the inventors have surprisingly discovered a hitherto before unknown property of the betaine. This property which has been newly discovered by the inventors relates to using betaine to increase the resistance of pigs to mycoplasmal infections,  
15 and/or to reduce the damage to pigs caused by the mycoplasmal infection or infections from other organisms.

The results of recent experiments have demonstrated that betaine plays a much larger role in the metabolism of animals, particularly in combating mycoplasmal infections and the damage caused by such infections  
20 in animals, particularly pigs, than would have been expected or could have been predicted, and consequently the inventors have discovered the use of betaine has now resulted in quite large but totally unexpected improvements in the growth rate and other performance characteristics of growing pigs when exposed to mycoplasmal infections or related organisms by the animals  
25 exhibiting an increase in resistance to mycoplasmal infection and a reduction in damage caused by such infections when the pigs are infected.

Therefore, it is an aim of the present invention to provide a method of and/or treatment for enhancing an animal's resistance to mycoplasmal infection or related organisms and/or reducing the amount of damage done to  
30 the animal by the infection through the use of betaine or equivalent material.

According to one aspect of the present invention there is provided a prophylactic against mycoplasmal infection or infection by related organisms in animals, which prophylactic reduces the chances of an animal contracting a mycoplasmal or related infection and/or reduces the damage caused to the  
35 animal by being infected with the mycoplasmal or related infection.

According to another aspect of the present invention there is provided a method of treating an animal to reduce the chances of being infected by a mycoplasmal or related infection or to reduce the amount of damage caused to the animal by the mycoplasmal or related infection when  
5 infected, comprising administering a therapeutic amount of prophylactic to the animal sufficient to counteract the effects of the mycoplasmal or related infection.

According to another aspect of the present invention there is provided a method of combating the effects of mycoplasmal or related  
10 infection in an animal, particular a pig, comprising administering a predetermined amount of a prophylactic or other disease fighting or disease reducing material to the animal for at least a predetermined time over a preselected period in order to effectively reduce or relieve the effect of or susceptibility to mycoplasmal or related infection.

15 Typically, the animal which can be treated by the prophylactic of the present invention is any animal, including humans. More typically, the animal is a pig, particularly a growing pig. Even more typically, the pig is less than 90 days old and/or less than 110 kg in weight.

Typically, the prophylactic is a betaine or a related compound.  
20 More typically, the betaine prophylactic is a glycine betaine (oxyneurin) or other betaine member compound or analogue. Other betaines include proline betaine,  $\beta$ -alanine betaine, tryptophan betaine, histidine betaine, 2-mercaptohistidine betaine, homostachydrine (pipecolate betaine) and the like.

Other prophylactics include glycine, methylene glycine, dimethyl  
25 glycine, glutamic acid,  $\gamma$ -aminobutyric acid, trimethylamine  $\gamma$ -butyric acid, or the like.

Typically, the betaine is administered alone or in combination with one or more other materials. Typically, the other materials include additives such as enzymes, antibiotics, vaccines, vitamins, and other medicaments or  
30 other agents or auxiliaries, feed supplements, or the like.

Typically, the other material or materials can be added separately or in combination with the betaine. Even more typically, the betaine and other material have a synergistically beneficial effect on the animal to protect it from mycoplasmal or related infection and the damage caused by such infection.

35 Typically, the feed administered to the pigs contains upto about 10.0 kg betaine or more per tonne of feed, more typically up to about

5.0 kg/tonne, more typically from 0.5 to 3.0 kg/tonne and preferably 1.0 to 1.25 kg/tonne.

Typically, the betaine or equivalent compound is included in the feed supplement in a first amount for feeding to the animals for up to 41 days, more typically up to 35 days, typically a grower feed which is fed to the animals initially, and in a second amount for feeding to the animals over the next up to 50 days, more typically 28 days, typically in a finisher feed. Typically, the first amount and second amounts can be different or can be the same. Typically, the amounts are between about 1.0 kg/tonne and 1.25 kg/tonne. However, it is to be noted that the duration of the grower and finisher periods can be any length of time.

Typically, the betaine can be fed to the pigs at any time from birth to slaughter. More typically, the pigs are fed betaine from early in the grower phase to late in the finisher phase.

Typically, the compounds and treatments of the present invention combat the effects of mycoplasma-induced diseases or diseases induced by related organisms, such as diseases produced from infections by Mycoplasma hyopneumoniae, mycoplasma hyorhinis, Mycoplasma hyosynoviae and the like. Additionally, the treatment of the present invention is effective against other diseases which cause lung damage, such as for example, pneumonias caused by other causes, dysentery, diseases caused by campylobacter and the like.

Typically, the prophylactic of the present invention is useful against agents that cause pneumonia lesions, such as for example, Mycoplasma, Pasteurella, Bordetella, Actinobacillus, Salmonella, Lungworms, Pseudorabies, Influenza, Migrating roundworm larvae, and the like.

The present invention will now be described by way of example with reference to the following example.

#### EXAMPLE 1

An investigation was carried out to determine the effect of adding betaine or a related or equivalent compound, either alone or in combination with another additive or auxiliary such as an enzyme, to the feed provided to selected groups of pigs as a prophylactic against mycoplasma-induced



diseases in pigs, such as diseases caused by Mycoplasma hyopneumoniae, Mycoplasma hyorhinis and Mycoplasma hyosynoviae, particularly mycoplasmal pneumonia.

Details of the trials conducted in this investigation were as follows:

5

#### Materials and Methods

Design: 2 x 2 factorial. The respective factors will be enzyme  
(zero and 1.0 kg/tonne) and betaine (zero and 1.25  
10 kg/tonne).

Animals required: 80 entire male pigs with an initial weight of 30.0 kg

15 Treatments: The four treatments will be designated as:

##### Grower (30 to 65 kg) (41 days)

A CGO Control male grower diet  
20 B CGP Control diet plus enzyme  
C CGB Control diet plus betaine  
D CGPB Control diet plus enzyme  
and betaine

25

##### Finisher (65 to 110 kg) (28 days)

E CFO Control male finisher diet  
F CFP Control diet plus enzyme  
G CFB Control diet plus betaine  
30 H CFPB Control diet plus enzyme  
and betaine

It is to be noted that pigs offered diets A, B, C and D above during  
the grower phase, which had a duration of the first 41 days, were also offered  
35 diets E, F, G and H respectively, during the finisher phase which extended  
over the next 28 days, which total the 69 days of the trial.

Duration: 69 days.

5      Feed Provided:      \* Both basal diets were based on wheat and mill mix  
                                 \* Basal grower diet was formulated to contain 13.4 MJ DE/kg and 0.65 g available lysine/MJ DE.  
                                 \* The diets were cold pressed into pellets.  
10                           \* The basal finisher diet was formulated to contain 13.0 MJ DE/kg DE and 0.50 g available lysine/MJ DE.  
                                 \* All diets were offered ad libitum.  
                                 \* Colour grits were included in each diet.

15      The measurements recorded during the 69 day trial were as follows:

Measurements:      1) Measurements of the weight of pigs were taken bi-weekly and P2 and tail fat thickness were measured at the same time.  
20                           2) Feed intake.  
                                 3) Feed:gain.  
                                 4) Final weight.  
                                 5) Carcass weight.  
25                           6) HC P2 and calliper P2.  
                                 7) Dressing percentage.  
                                 8) Carcass length.  
                                 9) Midline back fat thickness including the tail.

### Results

30                      The results for growth performance of pigs fed with a diet supplement including the betaine (Group C) were compared with pigs which were not fed with betaine (Group A) during the grower phase of the experiment (0 to 41 days) and are given in Table 1. The result for a similar comparison for the intermediate stages of the grower phase are given in Table  
35      2, and the results for the finisher period (41 to 69 days) are given in Table 3.

During the various stages of the grower phase of the experiment, betaine had a significant positive effect on growth rate and improved feed:gain in the period 1 to 28 days. Although the positive effects of betaine on growth performance tended to decline with time, betaine did improve growth rate during the 28 day finisher period and was most effective during the last two weeks of the period. The later period coincided with exposure to mycoplasma and it appeared that pigs offered the diets supplemented with betaine were less affected by the disease. Lung damage scores which were taken on all pigs at slaughter also tended to be lower in pigs offered the diet supplemented with betaine.

Some of the pigs involved in the trial were affected by mycoplasmal pneumonia during the finisher period of the trials, i.e. after about day 41 of the trial. These animals exhibited extremely low feed intakes and growth rates. The pigs used in the trial were examined for lung damage at the time of slaughter after about 69 days of being fed with one of the diets referred to previously, and the amount of damage to the lungs caused by the mycoplasmal infection was recorded as lung damage scores. The lung damage scores are provided in Table 4 and relate to the percentage of lung area damaged by mycoplasmal infection.

As can be seen from the results of Table 4, the control groups of pigs (the group fed diets A and E), which were fed with the normal feed stock only and no betaine or enzyme either alone or in combination, developed a lung damage score of 12.4. The group of pigs which were fed with the normal feed stock plus 1.0 kg/tonne of enzyme (the group fed diets B and F) developed a lung damage score of 8.3. The remaining two groups of pigs which were fed the normal feed stock plus 1.25 kg/tonne of betaine (the group fed diets C and G) and the normal feed stock plus 1.25 kg/tonne of betaine and 1.0 kg/tonne of enzyme (the group fed diets D and H) developed lung damage scores of 6.1 and 6.3 respectively which is significantly below the lung damage scores of both groups which were not fed with betaine, being groups 1 and 2, with scores of 12.4 and 8.3 respectively. Thus, the inclusion of betaine, either with or without another additive such as the enzyme being present, clearly reduces the chances of mycoplasmal infection and/or the amount of damage caused by such, infection and therefore provides an effective treatment to combat the effects of these insidious diseases, particularly mycoplasmal pneumonia.

The administration of betaine either alone or in combination with an additive or auxiliary such as an enzyme, did improve growth rate during the 28 day finisher period and was most effective during the last two weeks of the period. The latter period coincided with the development of symptoms due to the infection and the results of the trial demonstrate that the pigs offered the diets supplemented with betaine either alone or in combination with other additives or auxiliaries were less affected by the disease than pigs which were not fed with betaine. Lung scores which were taken on all pigs at slaughter also tended to confirm that the amount of lung damage was lower in pigs offered the diet supplemented with betaine.

Betaine enhances the growth performance of animals, particularly pigs, by altering the nutrient supply to the animals, such as for example to the tissues of the pigs. It does this by altering the partition or distribution of nutrients between the different tissues of the animal, such as for example muscle tissues and organs, and by having different utilisation rates of the nutrients at different locations in the body by favouring utilisation rates at the tissue level. In addition, pigs fed with appropriate dosages of betaine, either with or without other additives or auxiliaries being present, exhibit increased resistance to contracting mycoplasma-induced diseases and when pigs do contract such diseases they have less serious bouts of disease as well as suffering less damage to their lungs from the disease.

The described arrangement has been advanced by explanation and many modifications may be made without departing from the spirit and scope of the invention which includes every novel feature and novel combination of features hereindisclosed.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is understood that the invention includes all such variations and modifications which fall within the spirit and scope.

TABLE 1

Effects of betaine on the performance of male pigs offered feed ad libitum during the period 0 - 14, 0 - 28 and 0 - 41 days (grower period)

5	<u>Betaine (kg/tonne)</u>	<u>0</u>	<u>1.25</u>
10	0 - 14		
	Daily gain (g)	961	1018
	Feed intake (kg/d)	1.59	1.62
15	Feed:gain	1.66	1.59
	0 - 28		
20	Daily gain (g)	971	1028
	Feed intake (kg/d)	1.83	1.83
	Feed:gain	1.88	1.78
25	0 - 41		
	Daily gain (g)	1010	1063
30	Feed intake (kg/d)	1.99	2.00
	Feed:gain	1.97	1.87

TABLE 2

Effects of betaine on the performance of male pigs offered feed ad libitum during the period 14 - 21 and 28 - 41 days (grower period)

5	<u>Betaine (kg/tonne)</u>	<u>0</u>	<u>1.25</u>
10	14 - 28		
	Daily gain (g)	971	1028
	Feed intake (kg/d)	1.83	1.83
	Feed:gain	1.80	1.78
15	28 - 41		
	Daily gain (g)	1098	1137
	Feed intake (kg/d)	2.34	2.37
20	Feed:gain	2.18	2.04

TABLE 3

Effects of betaine on the performance of entire male pigs offered feed ad libitum during the periods 41 - 55 and 41 - 69 days (finisher period)

5	<u>Betaine (kg/tonne)</u>	<u>0</u>	<u>1.25</u>
10	41 - 55		
	Daily gain (g)	910	904
	Feed intake (kg/d)	1.89	1.89
15	Feed:gain	2.08	2.10
	41 - 69		
20	Final weight (kg)	95.8	99.1
	Daily gain (g)	833	910
	Feed intake (kg/d)	1.97	2.06
25	Feed:gain	2.37	2.26

TABLE 4		
Lung Damage Scores		
30	Group	% of lung area damaged by mycoplasmal infection
	Fed diets A + E	12.4
	Fed diets B + F	8.3
	Fed diets C + G	6.1
35	Fed diets D + H	6.3

## Claims

1. A method for enhancing an animal's resistance to infection by mycoplasma or other organisms causing similar damage and/or reducing the amount of damage done to the animal by the infection, characterized by administering a therapeutic amount of a prophylactic, which is a betaine or a related compound, to the animal sufficient to counteract the effects of said infection.
2. The method according to claim 1, characterized in that the animal is a husbandry animal.
3. The method according to claim 1, characterized in that the animal preferably is a pig, most preferably a growing pig.
4. The method according to claim 1, characterized in that the prophylactic agent is glycine betaine or other betaine compound, such as proline betaine,  $\beta$ -alanine betaine, tryptophan betaine, histidine betaine, 2-mercaptohistidine betaine, homostachydrine and the like.
5. The method according to claim 4, characterized in that the prophylactic agent preferably is glycine betaine.
6. The method according to claim 1, characterized in that the prophylactic agent is glycine, methylene glycine, dimethyl glycine, glutamic acid, gammaaminobutyric acid, trimethylamine gamma-butyric acid, or an equivalent compound.
7. The method according to any of claims 1 - 6, characterized in that the prophylactic agent is administered alone or in combination with one or more other materials.
8. The method according to claim 7, characterized in that the other materials are additives, such as enzymes, antibiotics, vaccines, vitamins, or other medicaments, auxiliaries, or feed supplements.
9. The method according to claim 6 or 7, characterized in that the prophylactic agent and the other material have a synergistic effect in protecting the animal from mycoplasmal or related infections or the damage caused by such infection.
10. The method according to any of claims 1 - 9, characterized in that the prophylactic agent is used in an amount of up to about 10.0 kg or more per tonne of feed, preferably in an amount of up to about 5.0 kg/tonne,



more preferably from 0.5 - 3.0 kg/tonne and most preferably 1.0 - 1.25 kg/tonne.

11. The method according to claim 10, characterized in that in a first amount of the prophylactic agent is used in a grower feed for feeding a young  
5 animal and a second amount is used in a finisher feed for feeding the animal during a finisher period.

12. The method according to any of claims 1 - 11, characterized in that it is a method of prophylaxis or treatment of infections causing damage to lungs, membranes or joints.

10 13. The method according to any of claims 1 - 12, characterized in that it is a method of prophylaxis or treatment of infections caused by *Mycoplasma* bacteria, such as *Mycoplasma hyopneumoniae*, *Mycoplasma hyorhinis*, *Mycoplasma hyosynoviae*.

14. The method according to any of claims 1 - 13, characterized in  
15 that it is a method of prophylaxis or treatment of lung lesions, pneumonia or arthritis.

15. A prophylactic agent against infection by mycoplasma or other organisms causing similar damage in animals, characterized by comprising a betaine or a related compound.

20 16. A prophylactic agent, which is a betaine or a related compound, for use to defend or protect an animal from being infected by mycoplasma and other organisms causing similar damage.

17. Animal feed composition comprising a prophylactic agent, which is a betaine or related compound, in a sufficient amount for enhancing the  
25 animal's resistance to infection by mycoplasma or other organisms causing similar damage and/or reducing the amount of damage done to the animal by the infection.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/00284

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC6: A61K 31/205, A23K 1/16 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: A61K, A23K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CA, WPI		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9738686 A1 (HÄUSSINGER, DIETER), 23 October 1997 (23.10.97) --	1-17
X	US 5516798 A (PETER R. FERKET), 14 May 1996 (14.05.96), column 1, line 36 - line 42; column 4, line 54 - line 65, the claims --	1-17
X	WO 9424886 A1 (CULTOR LTD.), 10 November 1994 (10.11.94), page 3, line 6 - line 9; page 2, line 1 - line 4, claims 34-37 --	1-17
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
1 July 1998		06-07-1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer  Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/00284

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1992:543434, Yakult Honsha Co., Ltd.: "Pharmaceuticals effective in controlling Shigella infection", JP,A2,04126098, 920427, Heisei --	1-17
X	WO 9632850 A1 (CULTOR LTD.), 24 October 1996 (24.10.96) --	15-17
X	WO 9114435 A1 (BRIGHAM AND WOMEN'S HOSPITAL), 3 October 1991 (03.10.91), page 20, line 19 - page 21, line 3, the claims --	15-17
X	EP 0781554 A1 (TAIHO PHARMACEUTICAL CO., LTD.), 2 July 1997 (02.07.97), page 4, line 23 - line 34, the claims --	15,16
X	GB 2091101 A (SIGMA-TAU INDUSTRIE ET AL), 28 July 1982 (28.07.82) --	15,16
P,A	WO 9746246 A1 (TOMIFARM S.R.L.), 11 December 1997 (11.12.97), page 3, line 19 - line 28, the claims ----- --	1-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI98/00284

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-14  
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-14 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT  
Information on patent family members

09/06/98

International application No.

PCT/FI 98/00284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 5516798 A	14/05/96	NONE	
WO 9424886 A1	10/11/94	AU 682354 B AU 6570594 A BR 9406511 A CN 1141581 A EP 0695127 A JP 8509372 T	02/10/97 21/11/94 09/01/96 29/01/97 07/02/96 08/10/96
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